Mutant LRRK2 toxicity in neurons depends on LRRK2 levels and synuclein but not kinase activity or inclusion bodies.

Journal: J Neurosci

Publication Year: 2014

Authors: Gaia Skibinski, Ken Nakamura, Mark R Cookson, Steven Finkbeiner

PubMed link: 24403142

Funding Grants: Common molecular mechanisms in neurodegenerative diseases using patient based iPSC neurons

Public Summary:
Examining the role of leucine-rich repeat kinase 2 (LRRK2) in Parkinson's disease.

Scientific Abstract:
By combining experimental neuron models and mathematical tools, we developed a "systems" approach to deconvolve cellular mechanisms of neurodegeneration underlying the most common known cause of Parkinson's disease (PD), mutations in leucine-rich repeat kinase 2 (LRRK2). Neurons ectopically expressing mutant LRRK2 formed inclusion bodies (IBs), retracted neurites, accumulated synuclein, and died prematurely, recapitulating key features of PD. Degeneration was predicted from the levels of diffuse mutant LRRK2 that each neuron contained, but IB formation was neither necessary nor sufficient for death. Genetic or pharmacological blockade of its kinase activity destabilized LRRK2 and lowered its levels enough to account for the moderate reduction in LRRK2 toxicity that ensued. By contrast, targeting synuclein, including neurons made from PD patient-derived induced pluripotent cells, dramatically reduced LRRK2-dependent neurodegeneration and LRRK2 levels. These findings suggest that LRRK2 levels are more important than kinase activity per se in predicting toxicity and implicate synuclein as a major mediator of LRRK2-induced neurodegeneration.